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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,904	02/16/2001	Tae-Yoon Lee	12777.8US01	3661

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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
EINSMANN, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	6

DATE MAILED: 01/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,904	LEE ET AL.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 10/18/02, paper number 5. Claims 1-5 have been canceled and claims 6-9 have been added. Claims 6-9 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Tubercle and Lung Disease (1997) 78(1):13-19) in view of Taylor (Methods in Molecular Biology (1997) 70:273-278).

Lee et al. teach a method for detecting Mycobacterium tuberculosis using PCR amplification to amplify all or a portion of a 435 bp repeat sequence (p. 17-18). The repeat sequence is identical to instant SEQ ID NO: 2 (Fig. 4), and the primers for amplification were obtained from within this repeat sequence (p. 17). This repeat sequence is a portion of instant SEQ ID NO: 1, thus it is inherently a portion of the REP13E12 repeated sequence. Lee et al. teach that the 435 bp repeat sequence is found in Korean M. tuberculosis strains (Fig. 3).

The method taught by Lee et al. comprises the steps of:

isolating DNA from a clinical isolate or sample of body fluid (p. 18, "using DNA from either laboratory strains of the M. tuberculosis complex or culture positive clinical specimens");

contacting the isolated DNA under conditions suitable for amplifying a REP13E12 repeat sequence of the Korean strain of M. tuberculosis with primer sequences (p. 17-18, an inherent step in the PCR amplification undertaken by Lee et al.); and

assaying for amplified REP13E12 (p. 18, "Specific and constant PCR amplification products were observed").

Lee et al. do not teach a method wherein the primers comprise instant SEQ ID NO: 3 and instant SEQ ID NO: 4. Instant SEQ ID NO: 3 consists of nucleotides 300-317 of the repeat sequence taught by Lee et al. in Figure 3, and instant SEQ ID NO: 4 consists of the complement of nucleotides 511-528 of the repeat sequence taught by Lee et al.

However, methods for primer selection were routine in the art at the time the invention was made, and in fact a number of computer programs existed to assist scientists with primer selection. For example, Taylor discusses a software program called "GeneJockeyII" which generates primer pairs for a target sequence, allowing certain parameters to be selected by the practitioner. Taylor teaches that "GeneJockey can scan a given sequence to determine that areas of sequence are suitable to make primers for PCR (p. 274)."

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected primers from with in the 435 base pair region taught by Lee et al. to use in a detection assay for the detection of M. tuberculosis. The ordinary practitioner would have been motivated by the teaching of Lee et al. that "several primers based on the repeat

sequence" were used for PCR amplification and these assays resulted in specific and constant PCR amplification products when DNA from laboratory strains of clinical specimens was the target of interest (p. 17-18). The selection of any primers from within the 435 base pair region taught by Lee et al. and the use of such primers in amplification methods for the detection of M. tuberculosis are therefore obvious in view of the teachings of Lee et al. and the teachings of Taylor.

Response to Remarks

Applicant argues that Taylor is an inappropriate basis for a rejection under 103(a) because the claims recite particular primers while Taylor teaches only a computer program that can be used to identify primers, and that Taylor could not be used as enabling basis for the rejected claims. However, this argument is a piecemeal analysis of the rejection, which fails to consider the combination of the teachings of Lee et al. in view of Taylor. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Lee et al. provide an amplification method for the detection of M. tuberculosis in clinical samples, and teaches that several different primers were used. Lee et al. provide the nucleotide sequence of the repeat region and specifically teach that "the 435 bp repeat will be useful in designing PCR primers for the detection and classification of isolates of M. tuberculosis (p. 18)." Taylor provides a program that facilitates the selection of PCR primers. These teachings are combined in the rejection to provide a prima facie case that the selection of any set of primers from the 434 bp repeat sequence taught by Lee

et al. and using them in a PCR assay for the detection of M. tuberculosis is obvious, as is set forth in the rejection. The examiner is arguing that any primer pair selected from the sequence provided by Lee et al. would be a functionally equivalent primer pair to those used by Lee et al., including instant SEQ ID NO: 3 and SEQ ID NO: 4. In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the oligonucleotides used in the claimed methods simply represent structural homologues of the primer pairs used by Lee et al. concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the methods which utilized instant SEQ ID NO: 3 and SEQ ID NO: 4 are *prima facie* obvious over the cited reference in the absence of secondary considerations.

Applicant further argues that "unlike primers that could be generated by computer software" the experiments in the instant examples demonstrate that the primes employed in the present invention detect M. tuberculosis in clinical specimens. However, applicant provides no reasoning or evidence to support the assertion that primers selected by computer software using the repeat sequence as a template from which to select the primers would not detect M. tuberculosis in clinical specimens. In fact, the teachings of the prior art suggest that they would

since Lee et al. demonstrate that primers to this region were used to obtain "Specific and constant PCR amplification products (p. 18)." Absolute predictability is not required in order to establish an expectation of success. The MPEP states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness (2143.02)." No evidence has been provided which suggests that the methods which result when the teachings of Lee et al. are combined with Taylor would not work. Arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Applicant further asserts that the REP13E12-PCR method of the present invention has been demonstrated to be more accurate in detecting M. tuberculosis than conventional diagnostic methods or IS6110-based PCR methods. However, this assertion is only partially true based on the data provided in Table 2, which demonstrates that the sensitivity and specificity of the IS6110-PCR and the REP13E12 method are statistically the same (i.e. the specification states that "No statistical difference exists"). Furthermore, in order to overcome the prima facie case of obviousness, "Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope

with the claims (MPEP 716.02(b))." The IS6110-based PCR method is not the closest prior art to the instantly claimed invention. In fact Lee et al. in view of Taylor is the closest prior art.

Applicant argues that although Lee et al. describe the PCR amplification of a 453 base pair repeat sequence of M. tuberculosis, the reference does not contain any concrete data that the 453 base pair repeat sequence is useful for PCR detection of M. tuberculosis complex in clinical specimens. First, it is noted that the claims do not recite the detection of M. tuberculosis complex (which includes a number of species of Mycobacterium), but instead recite the detection of only M. tuberculosis. Second, Lee et al. teach that specific PCR products were observed using both laboratory strains or clinical specimens. Although Lee et al. do not provide data or PCR primers, they clearly teach the generic method and its feasibility for the detection of M. tuberculosis. The limitation wherein SEQ ID NO: 3 and SEQ ID NO: 4 are used as primers is addressed in the rejection.

For these reasons the rejection is maintained. Applicant is reminded that while a declaration in accordance with 37 CFR 1.132 or other evidence traversing rejections may be useful, applicant is reminded of the rules for timely filing of such a declaration or evidence set forth in MPEP 716.01.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Einsmann
Examiner
Art Unit 1634

January 2, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600